Medical Policy

Genetic Testing for Duchenne and Becker Muscular Dystrophy

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 512
BCBSA Reference Number: 2.04.86

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing for DMD gene mutations may be considered MEDICALLY NECESSARY under the following conditions:
- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female relatives:
  o To confirm or exclude the need for cardiac surveillance
  o For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy.

At-risk females are defined as first- and second-degree female relatives and include the proband’s mother, female siblings of the proband, female offspring of the proband, the proband’s maternal grandmother, maternal aunts, and their offspring.

Prior Authorization Information
Commercial Members: Managed Care (HMO and POS)
Prior Authorization is NOT required.

Commercial Members: PPO, and Indemnity
Prior Authorization is NOT required.

Medicare Members: HMO BlueSM
Prior Authorization is NOT required.

Medicare Members: PPO BlueSM
Prior Authorization is NOT required.

**CPT Codes / HCPCS Codes / ICD-9 Codes**
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81161</td>
<td>DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis and duplication analysis, if performed</td>
</tr>
<tr>
<td>81408</td>
<td>Molecular pathology procedure, Level 9 (eg, analysis of &gt;50 exons in a single gene by DNA sequence analysis)</td>
</tr>
</tbody>
</table>

### ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9 Diagnosis codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>359.1</td>
<td>Hereditary progressive muscular dystrophy (includes Duchenne muscular dystrophy)</td>
</tr>
<tr>
<td>359.22</td>
<td>Myotonia congenita</td>
</tr>
<tr>
<td>V26.31</td>
<td>Testing of female genetic disease carrier status</td>
</tr>
</tbody>
</table>

### ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G71.0</td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td>G71.12</td>
<td>Myotonia congenita</td>
</tr>
<tr>
<td>Z31.430</td>
<td>Encounter of female for testing for genetic disease carrier status for procreative management</td>
</tr>
</tbody>
</table>

**Description**

Mutations in the *DMD* gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases. The severe end of the spectrum includes the progressive muscle diseases Duchenne and Becker muscular dystrophy and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less and more severe forms, as well as identify female carriers at risk.

**Background**

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine phosphokinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, they are classified as Duchenne or Becker muscular dystrophy and when the heart is primarily affected, as *DMD*-associated dilated cardiomyopathy (left ventricular dilation and heart failure).
Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD), the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene. (1) The incidence of DMD is estimated to be 1 in 3,500 newborn male births, (2) and approximately one-third of DMD cases arise from new mutations and have no known family history. (1) Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool from years 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower’s sign, and difficulty climbing stairs. The affected child’s motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. The majority of patients will be wheelchair bound by ages 9 to 12 years but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (e.g. decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death. (1) Few individuals with DMD survive beyond the third decade.

Becker muscular dystrophy

Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-40s.

Female carriers

Females heterozygous for a DMD mutation can manifest symptoms of the disease. (3) An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from a mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy. (4) Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous women do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated DMD gene in the affected X chromosome. (5) In some cases, this compensation can be reversed by a non-random or skewed inactivation of X chromosome resulting in greater expression of the affected X chromosome and some degree of myopathic features. (6) Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the DMD gene and complete or partial absence of the X chromosome (Turner syndrome). (3)

Clinical diagnosis

DMD

The suspicion of DMD should be considered irrespective of family history, and is most commonly triggered by an observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or after the discovery of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs and getting up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties in rising from the floor or in tip-toe walking, and pseudo hypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and commonly a positive Gower sign. An elevation of serum creatine kinase, at least 10-20 times normal levels (between 5,000 and 150,000 IU/L), is non-specific to DMD but is always present in affected patients. (1) Electromyography and nerve-conduction were traditional parts of the assessment of neuromuscular disorders, but now these tests are no longer believed to be necessary for the specific assessment of DMD. (7) An open skeletal muscle biopsy is needed when a negative test for deletions or duplications to the DMD gene is negative. The biopsy will provide general signs of muscular dystrophy including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis on a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.
Becker muscular dystrophy (BMD) has a clinical picture similar to DMD but is milder than DMD and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5-100 times the normal level).

Molecular diagnosis

DMD is the only gene in which mutations are known to cause DMD, BMD and DMD-associated cardiomyopathy. Molecular genetic testing of DMD can establish the diagnosis of a dystrophinopathy without muscle biopsy in most patients with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males.

The gene that codes for dystrophin is the largest known human gene (1) A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex mutational spectrum with over 5,000 different reported mutations, as well as a high spontaneous mutation rate. (8)

Treatment of Duchenne Muscular Dystrophy

There is no cure for Duchenne or Becker muscular dystrophy, and treatment is aimed at control of symptoms to improve quality of life. However, the natural history of the disease can be changed by several strategies such as corticosteroid therapy, proper nutrition or rehabilitative interventions. Glucocorticoids can slow the loss of muscle strength and may be started when a child is diagnosed or when muscle strength begins to decline. (7) The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways. (1) Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at 2 to 5 years of age although there has been no demonstrated benefit of earlier therapy, before 5 years of age. (1)

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted toward specific mutations. (9) Several of these therapies are currently undergoing clinical trials with two of the most promising being anti-sense oligonucleotide induced exon-skipping and gene repair and replacement with an adeno-associated viral (AAV) vector. (10) Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. The result is a DMD protein that is formed without the mutated exon and a normal, non-shifted reading frame. Exon skipping may be able to restore DMD protein function so that the treated patient’s phenotypic expression more closely resembles BMD. Gene transfer using AAV vector therapy involves the transfer of a functional DMD gene to the patient using this nonpathogenic and low immune response vector. (11)

Summary

The analytic and clinical validity of genetic testing for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are high. DMD is the only gene in which mutations cause the dystrophinopathies, and molecular genetic testing can establish the diagnosis in most patients. Nearly all affected individuals will be found to have a DMD mutation, and false positives are expected to be rare.

The clinical utility of DMD gene testing can be established for the index case and for at-risk female relatives. For the index case, utility lies in confirmation of the diagnosis without a muscle biopsy, initiation of effective treatment, and in distinguishing between DMD and the less severe BMD. For at-risk female relatives, the test can confirm or exclude the need to undergo routine cardiac surveillance, and can indicate the likelihood of an affected offspring in women considering children.
Therefore, genetic testing for *DMD* gene mutations may be considered medically necessary to establish a diagnosis in a male with clinical signs and symptoms suggestive of a dystrophinopathy and as testing for at-risk female relatives.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
</tbody>
</table>

**References**